REMARKS

Introduction

This response is identical to the response filed on June 27, 2005 except that claims 8, 23 and 52 have been amended to recite the cells are targeted cells and the remarks identify that claims 67 to 86 are pending.

As an initial matter, applicants wish to thank Examiner Qian and her supervisor, Dave Nguyen, for the courtesies extended by them during an interview on April 12, 2005. The arguments and amendments in this response reflect the contents of that interview.

Receipt is acknowledged of a non-final office action dated March 25, 2005. In the action, the Examiner rejected claims 1, 4-8, 10-12, 14, 19, 23, 33, 50, 52, 65 and 66 allegedly for non-enablement and claims 1, 4-7, 8, 10-12, 14, 19, 23, 33 and 52 for obviousness reasons.

Applicants respectfully request reconsideration of the present application in view of the foregoing amendments and in view of the reasons that follow.

Status of the Claims

In this response, applicants canceled claim 50 and amended claims 1 and 33. Support for amended claims can be found throughout the specification (claims 1 and 33), and in particular, on page 42, line 24 to page 43, line 2, and on page 19, line 16 to page 20, line 11 (claim 1) of the specification.

In addition, applicants added new claims 67-84. Applicants respectfully assert that new method claims 67-84 are so integrally related to the presently claimed transgenic mouse that it would not be an undue burden for the Examiner to search the claimed methods. In fact, a search of the transgenic mouse would cover a search of the claimed methods (both the new and withdrawn method claims). Support for the new claims can be found in originally filed claims 1, 4-8, 10-12, 14, 18, 19, 23, 26-28, and 33. Upon entry of this amendment, claims 1, 4-8, 10-12, 14, 19, 23, 33, 52, and 65-86 will be under examination.

35 U.S.C. 112, first paragraph

Enablement

Claims 1, 4-8, 10-12, 14, 19, 23, 33, 50, 52. 65 and 66 were rejected under 35 U.S.C. § 112, first paragraph. The claims were rejected because the specification allegedly "does not reasonably provide enablement for any transgenic mouse comprising a cell comprising claimed transgenes" and "does not enable any transgenic mouse without any phenotype." Office Action at 3. In addition, the Office Action stated that "the claims do not recite any visible observable or detectable characteristic of the claimed mice other than their genotype" and "the essential elements of the claimed invention, [and] phenotypes of the claimed mice[] are not recited in the claims." Office action at 4.

Applicants respectfully assert that the present invention successfully provides for a ligand activated, site-specific, somatic recombination system that recombines an endogenous chromosomal DNA sequence (gene, intergenic sequence or other genomic region) in its natural chromatin environment and naturally belonging to the genome of a mouse, with high efficiency. The effect of such a recombination event (following a low dose administration of a synthetic ligand) is that the DNA sequence is conditionally deleted, inactivated, inverted, or replaced.

The DNA sequence of interest can be targeted by flanking the sequence with LoxP sites. Therefore, a great many DNA sequences can be conditionally recombined and an RXR gene is merely exemplary. In fact, submitted herewith are eight references which support this proposition:

Author	Title	
Benoit Chapelier, et al.	Physiological and retinoid-induced proliferations.....	The EMBO Journal, Vol. 21, No. 13, ppgs. 3402-3413; 2002
Takeshi Imai, et al.	Peroxisome proliferators-activated receptor	PNAS, Vol. 101, No. 13, ppgs. 4543-4547; 2004
Mei Li, et al.	Skin abnormalities generated by temporally controlled RXR	Nature, Vol. 407, ppgs. 633-636; 2000

Gordon W. McLean et al.	Specific deletion of focal adhesion kinase	Genes and Development, 18, ppgs. 2998-3003; 2004
Daniel Metzger, et al.	Targeted conditional somatic mutagenesis in the Mouse.....	KO of Retinoid Receptors, Vol. 22, ppgs. 379-407; 2003
Michael Schuler, et al.	Temporally controlled targeted somatic mutagenesis in skeletal	Genesis, 41:165, ppgs. 165-170; 2005
Philipp Weber, et al.	Germ cell expression of the transcriptional	Development, 129, ppgs. 2329-2337; 2002
Misc. Authors	References demonstrating that genes other than RXRα and cell types other than adipocytes work in the present invention	

Regarding the Office's remarks concerning phenotype, applicants respectfully assert that a phenotype is not always a visible, observable characteristic. While the mice of the present invention may demonstrate alopecia, diabetes, altered cell proliferation, altered lipid metabolism, etc., the mice described in the instant specification may not have a visible phenotype following a recombination event. However, this does not indicate that the inventive mice are not useful.

In other words, the mice described herein are suitable for studying/identifying the particular function of a gene. Thus, the absence of a visible phenotype following a recombination event indicates that a target gene has no function or may not be relevant for a particular physiological process. But this is, in actuality, also a phenotype.

Therefore, to more clearly define the present invention, the claims have been amended to recite that the phenotype is a result of site-specific targeted somatic recombination. The claims have also been revised to refer more clearly to a percent recombination efficiency corresponding to a number of cells having undergone DNA recombination expressed in percent targeted cells.

Therefore, based on the teachings in the present specification and the techniques known in the art, a skilled person would know how to make and use the claimed mice of the present invention.

Furthermore, claims 33 and 50 were rejected because "the specification only discloses crossing the transgenic mouse with another transgenic mouse" (office action at 5)

and "the specification does not teach the claimed mouse having phenotype of altered metabolism in adipocytes or that resembles of diabetes as recited in claim 50" (office action at 4), respectively. Applicants respectfully traverse this ground for rejection.

In the interest of expediting prosecution, applicants amended claim 33 to recite a Cre-ER mouse to more clearly define the present invention. Support for this amendment can be found throughout the specification. Regarding claim 50, applicants assert that page 41 of the present specification specifically describes that in one embodiment, the Cre-ER transgenic mouse of the present invention can cause "alteration of the metabolism of the lipids in the adipocytes and/or diabetes." Specification at 41, lines 4-11. Nevertheless, in the interest of expediting prosecution and without acquiescing to the Examiner's rejection, applicants canceled claim 50.

35 U.S.C. 103

Claims 1, 4, 5, 8, 10, 11, 19 and 33 were rejected under 35 U.S.C. § 103 as allegedly obvious over Feil *et al.* (*PNAS*, 93:10887 (1996). In addition, claim 6 was rejected as allegedly obvious over Feil, in view of Schwenk *et al.* (*Nucleic Acids Res.*, 26:1427 (1998)). Lastly, claims 7, 12, 14, 23 and 52 were rejected as allegedly obvious over Feil, in view of Indra *et al.* (*Nucl. Acid Res.* 27:4324-4327 (1999)), Ross *et al.* (*PNAS*, 87:9590 (1990)) and Tontonoz *et al.* (*PNAS*, 94:237 (1997)). Applicants respectfully disagree.

Applicants respectfully assert that the cited references do not describe a transgenic mouse with a system that (1) controls recombinase activity both spatially and temporally, (2) is highly efficient (at least 90% recombination efficiency) for recombining endogenous DNA sequences; and (3) requires only a low dose of a synthetic ligand to trigger a site-specific targeted somatic recombination in the nucleus of a cell. Thus, in the interest of expediting prosecution, applicants amended claim 1 to recite that the recombination occurs in less than 5% of the targeted cells in the absence of a synthetic ligand" and that the recombination efficiency is "at least 90% expressed in number of cells that actually undergo DNA recombination over 100 targeted cells, resulting in site-specific targeted somatic recombination upon administration of a low dose of the synthetic ligand." Support for this amendment can be found on page 42, line 24 to page 43, line 2, and on page 19, line 16 to page 20, line 11. Applicants trust that this amendment addresses the Examiner's concerns.

Finally, applicants wish to state that the invention does not concern an inducible system for producing a Cre recombinase fusion protein. On the contrary, the invention concerns a system for inducing recombinase activity upon treatment with tamoxifen. The Cre fusion protein is always expressed, but it is inactive in the absence of tamoxifen.

CONCLUSION

Applicants respectfully request reconsideration of the present application in view of the foregoing amendments and arguments.

It is respectfully urged that the present application is now in condition for allowance. Early notice to that effect is earnestly solicited.

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

Respectfully submitted,

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By _____

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